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TITLE: Management of Noncompressible Hemorrhage Using Vena Cava Ultrasound

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14. ABSTRACT
The Combat Casualty Care Research Program, through the JWMRP, is specifically interested in testing and refining techniques for early intervention in life-threatening battle injuries. The purpose of this study is to determine the utility of ultrasonic assessment protocol of inferior vena cava vena cava diameter and collapsibility to detect and aid in management of non-compressible hemorrhage in major trauma victims. During the initial year of this project, subcontracts to participating sites have been issued, local Institutional Review Board applications and protocol amendments have been submitted, research staff and clinician sonographers have been recruited and trained at three sites. The University of California San Diego and Virginia Commonwealth University have completed IRB and HRPO approvals and have screened (n=142) and enrolled patients (n=45). The University of Utah has IRB approval and has submitted to HRPO. Emory University has withdrawn from the study and a replacement site, University of Maryland has been identified. There are no major finding or results at this time.

15. SUBJECT TERMS
Trauma; hypovolemia; inferior vena cava; IVC; internal jugular; IJ; collapsibility; injury; ultrasound; hemorrhagic shock

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Introduction:
The National Trauma Institute (NTI) proposed to utilize $ 498,269 in Joint Warfighter Medical Research Program Funding to extend the work previously completed at academic trauma centers using bedside ultrasound to identify patients with evidence of hypovolemia as determined by inferior vena cava (IVC) and internal jugular (IJ) collapsibility. Prior small studies of ultrasonographic assessment of IVC and IJ diameters and collapsibility demonstrated it to be a sensitive detector of blood volume loss and hemorrhagic shock. The specific aims of this study are: (1) determine the sensitivity, specificity and accuracy of ultrasonic assessment (USA) of IVC diameters in detecting traumatic shock at admission as compared to vital signs, (2) determine the ability of USA of IVC diameters to detect preclinical shock states defined by elevated arterial blood gas (ABG) Base Deficit or lactate in trauma patients without hypotension (SBP less than 90) at admission, (3) correlate the restoration of IVC diameters and collapsibility to achievement of endpoints of shock resuscitation in the ICU, such as correction of Base Deficit or lactate, evidence of improved organ perfusion such as urine output, limited echocardiography and avoidance of multiple organ dysfunction or death. The initial four clinical sites for this study are University of California at San Diego (UCSD), Virginia Commonwealth University (VCU), University of Utah (Utah), Emory University at Grady Memorial Hospital (Emory).

Keywords:
Trauma; hypovolemia; inferior vena cava; IVC; internal jugular; IJ; collapsibility; injury; ultrasound

Accomplishments:
The major goals of this project as identified in the Statement of Work are below with percent completion determinations and completion dates as appropriate.

Aims and Major Goals	**Timeline in Months**	**Actual completion date**	**% of completion**
Specific Aim 1: Prepare for Clinical Trial			
If Applicable, coordinate with Sites for CRADA* submission	1-3	N/A	N/A
If Applicable, coordinate with Sites for material transfer agreements (MTAs) or clinical trial agreements (CTAs) submission	1-3	N/A	N/A
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	17/09/2015	100%
Finalize consent form & human subjects protocol	1-3	17/09/2015	100%
Coordinate with Sites for IRB** protocol submission	1-3	01/10/2015	100%
Coordinate with Sites for UCSD IRB review	1-6	06/07/2016	100%
Start-up activities	1-6		75%
Coordinate with Sites for Military 2nd level IRB** review (ORP/HRPO)	1-6		50%
Submit amendments, adverse events and protocol deviations as needed	As Needed	//	0%
Coordinate with Sites for annual IRB** report for continuing review	Annually	//	0%

*Milestone Achieved: Local IRB** approval at VCU, Utah and Emory*	1-6		66%
*Milestone Achieved: HRPO*** approval for all protocols*	6		50%
*Milestone Achieved: local IRB** approval for all protocols through UCSD.*	6	06/07/2016	100%
Specific Aim 2: Coordinate Study Staff for Clinical Trial			
Sites identify or hire SRAs, Train clinician sonographers	3-6		75%
Milestone Achieved: Research staff trained	3-6		75%
Specific Aim 3: Randomized Controlled Trial - Conduct Study, Report Findings			
(1) determine the sensitivity, specificity and accuracy of ultrasonic assessment (USA) of IVC diameters in detecting traumatic shock at admission as compared to vital signs, (2) determine the ability of USA of IVC diameters to detect preclinical shock states defined by elevated arterial blood gas (ABG) Base Deficit or lactate in trauma patients without hypotension (SBP less than 90) at admission, (3) correlate the restoration of IVC diameters and collapsibility to achievement of endpoints of shock resuscitation in the ICU, such as correction of Base Deficit or lactate, evidence of improved organ perfusion such as urine output, limited echocardiography and avoidance of multiple organ dysfunction or death.	6-24		10%
Demonstrate equivalency of pocket ultrasound devices for IVC exam	12-18		
Milestone Achieved: 1st participant consented, screened and enrolled in study	6	29/07/2016	100%

During the reporting period, the PI at the lead site (Jay Doucet at USCD) confirmed no CRADAs, CTAs or MTAs were needed between sites. Dr. Doucet completed the human subjects protocol and consent document and obtained IRB approval for all sites. To complete the study in two years will require 4 trauma centers contributing about 125 study patients each for a total of 500 study subjects. UCSD and VCU have received HRPO authorization to proceed and are enrolling. To date, UCSD has screened 105 subjects and enrolled 8 subjects. VCU has screened and enrolled 37 subjects. Dr. Doucet held a teleconference with all sites to coordinate 3 sites IRB approvals and Military 2nd level reviews. Training of research staff and sonographers has been conducted at UCSD, VCU and Utah which included research ethics, consent procedures and IVC and IJ ultrasound examinations. The following protocol changes, as recommended by the NTI Science Committee, were implemented:

1. Define patients of interest with specific inclusions and exclusions
2. Specify timing of Inferior Vena Cava (IVC) measurements and limit to only two with deletion of the proposed 24 hour sample.
3. Record volume of fluid infused and relate that to IVC changes.
4. Relate IVC changes to 2 primary endpoints e.g. hemostatic interventions. Include secondary endpoints but only a reasonable number with definition of what will be considered a positive result.

5. Compare IVC changes with the current standard of care measurement used for predicting the need for hemostatic intervention.
6. Recruit additional study sites.
7. Determine inter-rater variability and how it will be controlled.

UCSD, VCU, Utah and Emory are the initial sites for this project. However, Emory recently withdrew from the project (08 Aug 2016) due to internal research infrastructure limitations. University of Maryland (UMD), which was participating site under the earlier project, has agreed to reopen the study to participate as the fourth site. A request for a modification of the Statement of Work for the site change will be submitted in the first quarter of Year 2.

With respect to training opportunities associated with this study, Dr. Doucet has produced "Protocol Video USA-IVC Study (Version 5)" that is posted on youtube: https://youtu.be/54-Z6fiJpPY This video describes study design and procedures, inclusion/exclusion criteria and includes a demonstration to train clinical sonographers on correct techniques to measure IVC diameter in research participants.

At this stage of the project, there are no results to disseminate to communities of interest.

Plans for the next quarterly reporting period include receiving HRPO approval for Utah and UMD and acknowledgement/approval of the change in the protocol and receiving approval for the site change. The research staff at University of Maryland will be trained on the protocol and imaging techniques. It is anticipated Utah and Maryland will begin enrollment in the next quarter.

Impact:
At this stage of the project, there has been no impact on the principal discipline, other disciplines, technology transfer, or society beyond science and technology**.**

Changes/Problems:
The National Trauma Institute Science Committee reviewed this project during their quarterly meetings and recommended modifications to strengthen the study. These recommendations were discussed with the PI at UCSD and were implemented but prompted no change in the Statement of Work as approved by the DoD. Changes eliminated the 8-24 hour FAST data point and added inclusion/exclusion criteria - one added due to non-obtainable images due to body habitus. Additionally, the changes eliminated Mortality and Base Deficit as secondary endpoints. An amendment request was approved by UCSD IRB on August 4, 2016.

As discussed previously, Emory opted not to participate in the current study. A replacement site, University of Maryland, has been identified and a request for Statement of Work modification will be submitted for this change. University of Maryland already has local IRB approval and is preparing to submit to HRPO in the next quarter.

Products:
Dr. Doucet has produced "Protocol Video USA-IVC Study (Version 5) that is posted on youtube: https://youtu.be/54-Z6fiJpPY This video contains study design, procedures, inclusion/exclusion criteria and a demonstration to train clinical sonographers on correct techniques to measure IVC diameter in research participants.

Participants & Other Collaborating Organizations:

Participants

Name	Project Role	Nearest person month worked	% Effort	Contribution to the project
Donald Jenkins	Principal Investigator	1	5%	Oversight of entire project
Roy Estrada	Program Manager	1	10%	Regulatory oversight and coordination of regulatory reviews and reporting
Monica Phillips	Research Operations Director	1	2.5%	Negotiated and executed subaward.

There are no changes in the active other support for the PI or key personnel.

Other Collaborating Organizations

Organization	Location	Contribution to Project
University of California San Diego	200 W Arbor Drive, #8896, San Diego, CA 92103	Lead clinical site, protocol design (PI: Jay Doucet, MD)
Virginia Commonwealth University	1200 Broad Street, Richmond VA 23298	Clinical site (PI: Paula Ferrada, MD)
University of Utah	30 North 1900 East, 3B110, Salt Lake City, UT 84132	Clinical site (PI: Ram Nirula, MD)
Emory University at Grady Memorial Hospital	69 Jesse Hill Jr. Drive, Glenn Memorial Bldg., Suite 307, Atlanta, GA 30303	Clinical site (PI: Chris Dente, MD)

Special Reporting Requirements:
The Quad Chart for this project follows:

Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography (USA-IVC)

ERMS/Log Number: JW140026
Award Number: W81XWH-15-2-0039

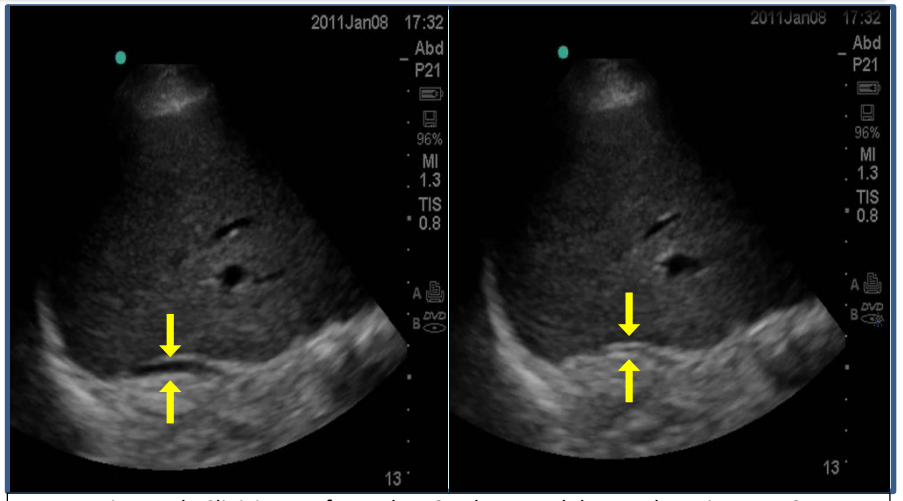
Grant PI: Donald Jenkins **PI:** Jay Doucet **Org:** UC San Diego **Award Amount:** $498,269

Study

1. Determine if ultrasonic assessment (USA) of Inferior Vena Cava (IVC) or Internal Jugular Vein (IJ) diameters is sensitive and specific in detecting hypovolemia at admission by predicting transfusion requirements.
2. Correlate the restoration of IVC diameters and collapsibility to achievement of endpoints of shock resuscitation in the ICU phase at 8-24 hours.

Approach

This is a randomized prospective clinical trial performed at 4 academic Level I trauma centers. Major trauma patients undergo a FAST abdominal ultrasound with USA of the IVC at admission and after minutes resuscitation. Patients with continued IVC collapse at the 2nd exam are considered Non-Responders to resuscitation. Their need for interventions and outcomes is compared to those with collapsible IVCs at admission that respond to initial resuscitation.



In our prior work, Clinician-performed FAST ultrasound detected persistent IVC Collapsibility in Major Trauma Victims which predicted 24 hour ongoing intravenous fluid requirements

Timeline

Activities CY	16	17
Patient Enrollment		
Develop standardized technique and training for USA-IVC exam		
Promulgate USA-IVC technique		

Goals/Milestones:

CY16-17 Goal – Patient Enrollment
☐ Start patient enrollment at 4 Level I Trauma Centers
CY17 Goal – Data Analysis
☐ Analyze data and disseminate findings via NTI meeting, abstract and peer review publication
CY17 Goal – Promulgate USA-IVC technique
☐ Develop learning tool kit to allow providers to learn USA-IVC technique and QA process, including for pocket sized ultrasound devices.

Updated: 10/07/2016